ON CERTAIN PECULIARITIES OF HYPERTENSION IN ITSENKO—CUSHING'S DISEASE AND PRIMARY (TUMOROUS) HYPERCORTICISM

E. K. Bozadjieva

High blood pressure is pointed out as one of the essential clinical signs of the condition in nearly all comprehensive studies on the Itsenko—Cushing syndrome (2,7,19). Nevertheless, systematic investigations in this direction cannot be found in the literature hitherto reviewed.

Plotz and assoc. (19) point out that hypertension in the Cushing syndrome exhibits high diastolic values and furthermore, that in cases of continuous hypertension enlargement of cardiac dimensions occurs. Vassiukova on her part states: „the cardio-vascular system in the symptomatic complex of the Itsenko—Cushing's disease deserves a particular attention, as the changes occuring therein determine the severity of the morbid condition and its course, and are moreover the most frequent cause for the lethal outcome. In addition, of all cardiovascular symptoms observed, an outstanding role is played by hypertension, usually exhibiting a course characterized by high systolic and diastolic values".

We made it our aim to investigate the peculiarities in the nature and course of hypertension accompanying the Itsenko—Cushing's disease and primary (tumorous) hypercorticism.

Material and Methods

The characteristic features of blood pressure were studied in 40 patients with diencephalic syndrome, running a course characteristic for the Itsenko—Cushing's disease (slight form), 225 patients with severe form of the Itsenko—Cushing's disease and 54 with primary (tumorous) hypercorticism, all of them undergoing treatment at the Therapeutical Dept. — all-Union Institute of Experimental Endocrinology in Moscow, over the period from 1947—1948 to the middle of 1962 inclusive (Table I). Twelve patients were also included, treated previously at the same Institute in whom the fundus oculi was investigated and the blood pressure accordingly measured. A major part of the patientes have been repeatedly treated at the Institute, some of them being followed up over a period of 8 and more years. The total number of patients amounts to 319. Of them 244 are females and 75 males, with a male to female ration 1 : 3.253, or women represented 76.5% of the total number, and men — 23.5%. The age of the patients ranged from 1 year and 6 months to 54 years. Thirty four patients were younger than 16 and 11 were beyond

the 50-year age limit. The greater part of the patients — 210 (66%) were aged from 20—40 years (Table 2). Twenty two of a total of 54 patients with corticoadrenal tumours, i. e. 41% were beneath 21 years of age, and merely one was older than 50.

The entire series was distributed into three groups: without raised blood pressure, with benign hypertension and with malignant hypertension. Blood pressure was considered increased when the diastolic pressure reached or exceeded 90 millimetres of mercury. Alterations in the fundus oculi were assumed as a criterium for distinction of malignant from benign hypertension, namely the presence of edema in the papilla or retina, hemorrhages and exudative changes in the retina, as it is universally accepted that edema of the papilla is the essential and one of the earliest diagnostical signs for the malignant phase of hypertension (8, 9, 12, 18, 23).

The results of the investigations were statistically elaborated (5). The systolic, diastolic and pulse pressure in individual groups of patients were comparatively evaluated with the mean values of blood pressure in the general population, of the respective age and sex, as well as with the blood pressure in groups of patients affected with ordinary benign hypertension, aged from 20—50 years and treated at the Naval Hospital — Varna during 1965.

The relationship between the type of hypertension and cardiac dimensions, severeness of proteinuria, osteoporosis manifestations and presence of diabetes was also investigated.

The statistical elaboration utilizes the methods of non-parametric, alternative and variation analysis. In the course of comparative evaluation of the height of blood pressure in our series with the normal levels for blood pressure in healthy persons (4), we aimed to find out: 1) what part of the patients were with blood pressure lower than normal for the respective age — sex group, established through P-50 (fiftieth percentile); 2) the number of patients with blood pressure between P-50 and P-75; 3) patients with blood pressure between P-75 and P-90 and 4) the number of patients with blood pressure exceeding P-90.

Theoreticalwise, the percentage ratio in the four groups listed should be 50 : 25 : 15 : 10. Every rather substantial deviation from the values indicated is a further corroboration of the fact that blood pressure in the patients investigated considerably differs from blood pressure in the healthy population.

We established, with the aid of alternative analysis, up to what extent was the difference between the percentages characterizing the various patients' groups characteristic. For the purpose the „t" criterium was utilized and the probability related to its degree.

The methods of variation analysis were employed with a view to establishing the mean level of blood pressure in different cathegories of patients. The comparison was carried out with the aid of the „t" criterium. In a rather restricted number of patients the degrees were in addition freely computed.

Results

The distribution of the patients according to sex, type of hypertension and form of hypercorticism is illustrated in table 1. It is evident from the latter that 32 patients are free from hypertension (21 women and 11 men), 149 — with benign hypertension (119 females and 30 malles) and 138 — with

Table 1

Distribution of Patients according to Type of Disease, Characteristic Features of Blood Pressure and Sex

	Without hypertension		Benign hypertension		Malignant hypertension		Total		Total	%	%	Total %
	Women	Men	W	M	W	M	W	M		W	M	
Diencephalic syndrome	7	3	12	5	12	1	31	9	40	9.72	2.76	12.54
Itsenko—Cushing's Disease	7	7	81	20	78	32	166	59	225	52.03	18.5	70.53
Tumorous Hyperadrenocorticism	7	1	26	5	14	1	47	7	54	14.7	2.2	16.93
Total	21	11	119	30	104	34	244	75	319	76.49	23.51	100
	32		149		138		319		319			
%	10		46.7		43.3		100					

malignant hypertension (104 females and 34 males), or the same figures expressed in percentages, they are accordingly: without hypertension — 10% of the patients, with benign hypertension — 46.7% and with malignant hypertension — 43.3%.

On comparing the percentage of the patients with benign and malignant hypertension, it was found that „t" is equal to 0.6, $P < 0.5$, which indicates that there is no essential difference in the distribution between benign and malignant hypertension in hypercorticism.

Out of a total of 75 men, 34 (or 45.3%) are affected with malignant hypertension, whereas out of a total of 244 women, 104 are with malignant hypertension (42.62%). The difference in the percentages ($t = 0.4$, $P < 0.5$) is not significant, or in other words men and women as well, affected by hypercorticism, are also equally affected by malignant hypertension (Table 2).

The data derived from the comparison of the type of hypertension in the various forms of hypercorticism and the duration of the disease are sum-

Table 2

Distribution of the Patients According to Age, Sex and Form of Hyperadrenocorticism

	Years		0—10	11—20	21—30	31—40	41—50	51—60	Total
Diencephalic syndrome	Without hypertension	women	—	2	1	4	—	—	7
		men	—	3	—	—	—	—	3
	Benign hypertension	women	—	1	2	7	2	—	12
		men	—	1	1	1	1	1	5
	Malignant hypertension	women	—	1	3	6	2	—	12
		men	—	—	1	—	—	—	1
Itsenko—Cushing's syndrome	Without hypertension	women	—	1	3	2	1	—	7
		men	1	2	3	1	—	—	7
	Benign hypertension	women	—	5	32	34	8	2	81
		mon	2	7	4	7	—	—	20
	Malignant hypertension	women	3	6	24	27	12	6	78
		men	1	7	9	12	2	1	32
Tumorous Hypercorticism	Without hypertension	women	1	2	1	3	—	—	7
		men	—	—	1	—	—	—	1
	Benign hypertension	women	7	4	5	7	2	1	26
		men	1	—	1	3	—	—	5
	Malignant hypertension	women	3	3	3	2	3	—	14
		men	1	—	—	—	—	—	1
	Total		20	45	94	116	33	11	319

marised in table 3. The analysis of the latter reveals that the duration of benign and malignant hypertension in women with diencephalic syndrome is greater as compared to the duration in cases with a course free of hypertonia; it is furthermore established that malignant and benign hypertensions do not differ significantly in this respect.

An essential difference insofar duration of the disease is concerned is not marked among the group of women affected with the Itsenko—Cushing's disease neither in benign and malignant hypertensions, nor in instances with a course not revealing increased blood pressure. In male patients with Itsenko-Cushing's disease, the malignant hypertension exhibits a rather protracted course as compared to benign cases. Benign hypertension in females also appears to be with a rather longer duration as compared to males affected with the Itsenko — Cushing's disease.

In tumorous hypercorticism, malignant hypertension in women is substantially more prolonged than benign.

It is our impression also, that in women with diencephalic syndrome without blood pressure rise the disease exhibits a longer duration as compared

Table 3

Dependence of Hypertension in Hypeadrenocorticism upon the Duration of the Disease

		Itsenko—Cushing's disease				Tumorous hyperadrenocorticism				Diencephalic syndrome			
		n	M±σ	t	P	n	M±σ	t	P	n	M±σ	t	P
Women	without hypert.	7	5±3	0,87	<0,5	7	3±2	1,2	≈0,2	7	5±3	2,11	≈0,05
	benign hypert.	81	6±4			26	2±2			12	9±5		
	without hypert.	7	5±3	1,64	≈0,1	7	3±2	1,64	<0,2	7	5±3	2	≈0,05
	mal. hypertens.	78	7±4			14	5±4			12	9±5		
	benign hypert.	81	6±4	1,52	≈0,1	26	2±2	2,83	<0,01	12	9±5		
	mal. hypertens	78	7±4			14	5±4			12	9±5		
Men	without hypertension	7	6±4	0,6	≈0,5								
		20	4±3										
	without hypertension	7	6±4										
	mal. hypertens.	32	6±4										
	ben. hypertension	20	4±3	2,0	<0,05								
	mal. hypertension	32	6±4										
	without hypertension women	7	5±3	0,4	>0,5								
	men	7	6±4										
	benign hypertension women	81	6±4	2,3	≈0,02	26	2±2	0,8	<0,5				
	men	20	4±3			5	3±3						
	malignant hypertension women	78	7±4	1,2	≈0,2								
	men	32	6±4										

		without hypertension				benign hypertension				milignant hypertension			
		n	M±σ	t	P	n	M±σ	t	P	n	M±σ	t	P
Women	diencephalic s;	7	5±3			12	9±5	2,0	<0,05	12	9±5	1,21	%0,2
	Its.—Cush. dis.	7	5±3			81	6±4			78	7±4		
	diencephalic s.	7	5±3	2,14	≈0,05	12	9±5	4,6	<0,001	12	9±5	2,16	<0,05
	tum.hyperadrenocorticism	7	3±2			26	2±2			14	5±4		
	Its.—Cush. disease	7	5±3	2,14	≈0,05	81	6±4	6,0	<0,001	78	7±4	1,9	≈0,5
	tum.hyperadrenocorticism	7	3±2			26	2±2			14	5±4		
Men	dienceph. syndr.					5	7±6	1,0	<0,5				
	Its.—Cush. syndr.					20	4±3						
	diencephalic syndrome					5	7±6	1,24	<0,5				
	tum.hyperadrenocorticism					5	3±3						
	Its.—Cush. syndr.					20	3±3	0,7	≈0,5				
	tum.hyperadrenocorticism					5	3±3						

to tumorous hypercorticism without elevation of blood pressure. Tumorous hypercorticism without increased blood pressure in women is with shorter duration as compared to the duration of the disease in the same group of the Itsenko—Cushing's syndrome. The benign hypertension in women with diencephalic syndrome is likewise characterized by a longer course as compared to benign hypertension in women affected with the Itsenko—Cushing's disease. In general, benign hypertension in the diencephalic syndrome in women is distinguished by a protracted course of the condition as compared to the duration in female patients with benign hypertension, due to the Itsenko—Cushing's disease and tumorous hypercorticism. Anyway, a difference in the continuity of the disease among women affected with diencephalic syndrome with benign hypertension, and those affected by the Itsenko—Cushings' disease and tumorous hypercorticism with malignant hypertension is not established. Rather more protracted is the duration of the condition in women affected by Itsenko—Cushing's disease with benign hypertension as compared to women affected by tumorous hypercorticism. Malignant hypertension in females with diencephalic syndrome is likewise distinguished by a prolonged duration of the affection as compared to women with tumorous hypercorticism. The same holds true for malignant hypertension in women with tumorous hypercorticism contrasted to females affected by the Itsenko—Cushing's disease, in whom the duration of the morbid process is longer.

The percentile method was utilised in the course of elaborating the normal limits (level) of blood pressure. Thus, 50% of the cases exhibit blood pressure beneath the mean value (P 50) and 50% show blood pressure values above P 50. Moreover, 25% of the total number of cases should be placed between the P50 and P75 percentiles, 15% of all cases — between P75 and P90 and 10% — beyond P90. The ratios just listed are observed among the population with normal blood pressure.

In order to find an answer to the question up to what extent the height of blood pressure among our patients differed from that in the healthy population, we proceeded as follows:

1. According to age and sex, the percentiles were established within which the blood pressure of the patients investigated was located.

2. The results obtained for each individual group of patients were summarized and illustrated in tables.

3. Computation was carried out of the percentage demonstrating the number of patients falling into the interval groups, enclosed within the respective percentiles.

The analysis of the tables compiled by the authors of the paper, shows that the blood pressure of the patients studied, both systolic and diastolic, is considerably higher than the blood pressure in the healthy population. As regards the pluse pressure a similar rule was not established.

The comparison of blood pressure (systolic, diastolic and pulse) in patients with various forms of hyperadrenocorticism with the mean blood pressure values for the respective age in the healthy population (4) showed that:

1. There is no essential difference in the systolic, diastolic and pulse pressures in women with Itsenko—Cushing's disease and normal blood pressure.

Table 4

Relationship Between Blood Pressure in Hyperadrenocorticism and Blood Pressure in Healthy Population

			Itsenko—Cushing's disease			Tumorous hyperadrenocorticism				Diencephalic syndrome			
			n	M±σ	t	P	n	M±σ	t	P	n	M±σ	t	P
Women	without hypertension	systolic pressure	7	117±18	0.57	≈0.5	7	114±13	1.03	<0.5	7	107±12	2.78	<0.02
			7	121± 4			7	120± 6			7	120± 4		
		diastolic pressure	7	70± 8	1.15	<0.5	7	71±12	0.17	>0.5	7	73±11	0	
			7	74±24			7				7			
		pulse pressure	7	47±18	0		7	42± 6	2	<0.1	7	33±11	3.26	<0.01
			7	47± 2			7	47± 3			7	47± 2		
	benign hypertension	systolic pressure	81	162±26	13.3	<0.001	26	156± 8	17.5	<0.001	12	154±27	3.75	≈0.001
			81	122± 6			26	114±10			12	124± 4		
		diastolic pressure	81	106±18	15.5	<0.001	26	104±17	0.25	<0.001	12	98± 9	7.74	<0.001
			81	75± 4			26	67± 9			12	76± 3		
		pulse pressure	81	54±17	3.7	<0.001	26	52±16	0.92	<0.5	12	57±22	1.37	<0.1
			81	47± 3			26	49± 3			12	48± 2		
	malignant hypertension	systolic pressure	78	164±35	10	<0.001	14	180±29	7.8	<0.001	12	167±50	3.04	<0.01
			78	124± 8			14	117± 7			12	123± 4		
		diastolic pressure	78	117±25	14	<0.001	14	128±30	6.5	<0.001	12	108±27	4.1	<0.001
			78	75± 5			14	71± 8			12	76± 2		
		pulse pressure	78	60±20	5.4	<0.001	14	52±19	0.6	≈0.5	12	59±26	1.58	<0.2
			78	40± 4			14	49± 3			12	47± 2		
Men	without hypertension	systolic pressure	7	122± 7	0.8	<0.5					3	107±12	2	<0.2
			7	119± 5							3	120± 1		
		diastolic pressure	7	76± 5	2.16	≈0.05					3	73± 6	1.07	<0.5
			7	69± 6							3	69± 3		
		pulse pressure	7	46± 6	1.15	<0.5					3	33± 6	4.7	<0.01
			7	49± 2							3	50± 3		
	benign hypertension	systolic pressure	20	155±22	7.1	<0.001	5	164±38	1.55	<0.1	5	171±37	2.6	<0.05
			20	118± 6			5	119±48			5	123± 3		
		diastolic pressure	20	109±21	7.8	<0.001	5	111±17	3.33	<0.02	5	104±19	2.9	<0.02
			20	70± 8			5	71±16			5	75± 5		
		pulse pressure	20	46±11	1.16	<0.2	5	53±19	0.6	<0.5	5	67±24	1.42	<0.2
			20	49± 2			5	47±2			5	50± 4		
	malignant hypertension	systolic pressure	32	183±32	10.5	<0.001								
			32	120± 2										
		diastolic pressure	32	131±26	13	<0.001								
			32	72± 2										
		pulse pressure	32	52±	2.42	<0.01								
			32	44± 5										

2. In male patients of the same group the diastolic pressure, although within normal limits, is higher than that of the normal population (Table 4).

3. No deviations whatever from the diastolic, systolic and pulse pressures of the population of the same age group are established in women with tumorous hyperadrenocorticism without hypertension (Table 4).

4. On the contrary, systolic pressure exhibits higher values than average for the normal population in patients with diencephalic syndrome (slight form of the Itsenko—Cushing's disease). Diastolic pressure in men is likewise higher, whereas in women the pulse pressure displays a minor amplitude (Table 4).

5. A substantial difference exists in the sense of higher values for systolic, diastolic and pulse pressure, than that in the normal population in women with Itsenko-Cushing disease associated to hypertension, both benign and malignant (Table 4).

6. A similar picture is seen in men merely for malignant hypertension and systolic and diastolic pressures in benign hypertension. The pulse pressure in the latter condition is insignificantly altered as compared to healthy population (Table 4).

It is worth mentioning that in diencephalic syndrome cases, in women and men alike, a substantial difference is noted in systolic and diastolic pressures both in benign and malignant hypertension, whereas for the pulse pressure such a difference is non existant (Table 4).

No substantial difference is established in systolic pressure on comparing the blood pressure in benign and malignant hypertension among females affected by Itsenko — Cushing's disease, whereas it is present insofar diastolic and pulse pressures are concerned. A significant difference is found in the systolic pressure also in males affected by the Itsenko—Cushing disease.

A substantial difference is established insofar systolic, diastolic and pulse pressures are concerned during comparative investigations of men and women with malignant hypertension, or in other words, the values of the pressures listed in malignant hypertension are substantially higher in men as compared to women (Table 5).

No significant difference is noted between the values of systolic and diastolic pressures in benign hypertension in men and women, affected by Itsenko — Cushing's disease. A difference is merely established in pulse pressure, which is lower in males, i. e. with a minor amplitude than in females.

Also, it is interesting to know that no significant difference is observed between the systolic, diastolic and pulse pressures in malignant and benign hypertension in the group of patients with diencephalic syndrome.

During the parallel investigation of blood pressure values in benign and malignant hypertension in men and women with hypercorticism and those in patients with common hypertonic disease (Table 6), the following facts attracted attention in particular:

1. In diencephalic syndrome cases there is no significant difference between benign hypertension in men and ordinary hypertonic disease.

2. There is no significant difference between the values of blood pressure in malignant hypertension in females with diencephalic syndrome and ordinary hypertonic disease, except for the pulse pressure, found to be substantially lower in patients with diencephalic syndrome.

Table 5

Relationship between Benign and Malignant Hypertension in the Itsenko—Cushing's Disease

			n	M±σ	t	P
Women	systolic pressure	malignant hypert. benign hypertens.	78 81	164±35.4 162±25.55	0.57	<0.5
	diastolic pressure	mal. hypertens. benign hypertens.	78 81	117±24.74 106±17.94	3.0	<0.001
	pulse pressure	malign. hypertens. ben. hypertension	78 81	60±19.80 54±16.58	2.07	<0.04
Men	systolic pressure	mal. hypertension benign hypertension	32 20	183±31.58 155±22.49	3.75	<0.001
	diastolic pressure	mal. hypertension benign hypertension	32 30	131±25.92 109±21.05	3.3	≈0.005
	pulse pressure	mal. hypertension benign hypertension	32 20	52±18.49 46±11.40	1.8	≈0.08
Malignant hypertension	systolic pressure	men women	32 78	183±31.58 164±35.4	2.75	<0.01
	diastolic pressure	men wonen	32 78	131±25.90 117±24.74	2.6	<0.01
	pulse pressure	men women	32 78	52±18.49 60±19.80	2.02	<0.05
Benign hypertension	systolic pressure	men women	20 81	155±22.49 162±25.55	1.23	<0.22
	diastolic pressure	men women	20 81	109±21.05 106±17.94	0.60	<0.55
	pulse pressure	men women	20 81	46±11.40 54±16.58	2.66	<0.01

3. Considerable difference in the sense of lower values, is observed in benign hypertension among females with diencephalic syndrome.

4. In women affected by Itsenko—Cushing's disease there is no difference between the diastolic pressure in benign and malignant hypertension and that in hypertonic disease. Systolic and pulse pressures in benign as well as in malignant hypertension are significantly lower.

5. Systolic and pulse pressures are substantially lower in men with benign hypertension, affected by Itsenko-Cushing disease, whereas diastolic pressure is analogous to that in hypertonic disease.

6. Systolic pressure in men with malignant hypertension, affected by Itsenko—Cushing disease does not differ from that in patients with hypertonic disease, whereas diastolic pressure is considerably higher, and pulse pressure—considerably lower.

In all instance of tumorous hyperadrenocorticism, the pulse pressure is substantialy lower than that in hypertonic disease. In benign hypertension cases, the systolic pressure is likewise lower among females, whereas in malignant hypertension the diastolic pressure is higher.

Table 9

Relationship between the Height of Blood Pressure in Benign and Malignant Hypertension in Hyperadrenocorticism and Height in Ordinary Hypertonic Disease

		Itsenko—Cushing's disease				Tumorous hyperadrenocorticism				Diencephalic syndrome			
		n	M±σ	t	P	n	M±σ	t	P	n	M±σ	t	P
Benign hypertension	systolic pressure	81 23	162±26 197±36	4.4	<0.001	26 23	156± 8 197±36	5.32	<0.001	12 23	154±23 197±36	4.0	<0.001
	diastolic pressure	81 23	106±18 111±13	1.53	≈0.1	26 23	104±17 111±13	1.6	<0.1	12 23	98± 9 111±13	3.3	<0.001
	pulse pressure	81 23	54±17 87±29	5.1	<0.001	26 23	52±16 87±29	5.0	<0.001	12 23	57±22 87±29	3.3	<0.001
Malignant hypertension	systolic pressure	78 23	164±35 197±36	4.0	<0.001	14 23	180±29 197±36	1.6	≈0.1	12 23	167±50 197±36	1.87	<0.1
	diastolic pressure	78 23	117±25 111±13	1.58	<0.2	14 23	128±30 111±13	2.02	<0.05	12 23	108±27 111±13	0.3	>0.5
	pulse pressure	78 23	60±20 87±29	4.15	<0.001	14 23	52±19 87±29	4.3	<0.001	12 23	59±26 87±29	2.8	<0.01
Benign hypertension	systolic pressure	20 31	155±22 181±28	3.7	<0.001	5 31	164±38 181±28	0.85	<0.5	5 31	171±37 181±28	0.5	>0.5
	diastolic pressure	20 31	109±21 105±16	0.70	<0.5	5 31	111±17 105±16	0.55	>0.5	5 31	104±19 105±16	0.1	>0.5
	pulse pressure	20 31	46± 4 75±19	7.2	<0.001	5 31	53±19 75±19	4.7	<0.001	5 31	67±24 75±19	0.7	<0.5
Malignant hypertension	systolic pressure	32 31	183±32 181±28	0.3	<0.05								
	diastolic pressure	32 31	131±26 105±16	4.6	<0.001								
	pulse pressure	32 31	52±18 75±19	5.0	<0.001								

Table 7

Distribution of Proteinuria according to Severity in Various Hypertension and Various Forms of Hyperadrenocorticism

			Absence of albuminuria	Albuminuria	High albuminuria	Total
Diencephalic syndromes	without hypertension	women	7	—	—	7
		men	3	—	—	3
	benign hypertension	women	9	3	—	12
		men	—	4	—	4
	malignant hypertension	women	3	5	1	9
		men	—	1	—	1
Itsenko Cushing's disease	without hypertension	women	4	3	—	7
		men	5	2	—	7
	benign hypertension	women	43	34	2	79
		men	8	9	1	18
	malignant hypertension	women	15	53	10	78
		men	8	17	7	32
Tumorous hyperadrenocorticism	without hypertension	women	—	6	—	6
		me	—	1	—	1
	benign hypertension	women	4	18	—	22
		men	2	3	—	5
	malignant hypertension	women	2	11	—	13
		men	—	1	—	1
	Total	113 (women 153 (men 26)		171 (women 133) (men)	21 (women 13) (men 8)	305 (women 234) (men 71)

The distribution of proteinuria in accordance with the type of hypertension and form of hyperadrenocorticism is illustrated in table 7. In our series, in 61% of the patients without blood pressure increase, in 47% of those with benign hypertension and in 21% of the cases with malignant hypertension, proteinuria was not disclosed. The difference between the three groups of patients was substantial (between the first and second $P < 0.01$, between second and third as well as between first and third $P < 0.001$). Heavy proteinuria was observed in 13.43% of the patients with malignant hypertension and merely in 2.14% of those with benign hypertension ($P<0.05$)

The dependence of cardiac dimension alterations upon the type of hypertension and form of hyperadrenocorticism is demonstrated in table 8. In 16% of the patients of our series without blood pressure rise, in 7% of the total number with benign hypertension and merely in 1.6% of those with malignant hypertension, hypertrophy of the heart was not encountered. The difference between the patients of first and third groups is rather significant ($P<0.001$).

The distribution of osteoporosis in compliance with the nature of hypertension and form of hyperadrenocorticism is demonstrated in table 9. It illustrates that severe osteoporosis is more frequently met in malignant hypertension (78% against 22% in benign cases, $P < 0.001$).

Table 8

Distribution of Alterations in the Cardiac Size According to Sex Type of Hypertension and Form of Hyperadrenocorticism

			Normal heart size	Enlarged heart size	Total number of patients investigated
Diencephalic syndrome	without hypertension	women	1	6	7
		men	—	3	3
	benign hypertension	women	—	11	11
		men	—	4	4
	malignant hypertension	women	—	12	12
		men	—	1	1
Itsenko-Cushing's disease	without hypertension	women	—	7	7
		men	—	6	6
	benign hypertension	women	—	79	79
		men	1	17	18
	malignant hypertension	women	—	71	71
		men	1	29	30
Tumorous hyperadrenocorticism	without hypertension	women	4	3	7
		men	—	1	1
	benign hypertension	women	9	14	23
		men	—	4	4
	malignant hypertension	women	1	12	13
		men	—	—	—
			17	280	297

Diabetes was observed in 20% of our series. The dependence of the latter condition upon the character of hypertension is not proved ($P<0.5$).

We have the impression furthermore, that severe osteoporosis and diabetes as well are rarely encountered in instances of diencephalic syndrome.

Discussion and Inferences

Although authors like Pickering emphasize the importance of systematic investigations of hypertension in hyperadrenocorticism cases insofar elucidation of the pathogenesis of hypertonic disease is concerned, relevant reports in the literature are not found.

According to Mills (14), increased blood pressure is established in 85% of all patients with Cushind's syndrome. Raker and assoc. (20) found arterial hypertony with diastolic pressure exceeding 100 millimeters of mercury in 51 (81%) out of a series comprising 63 patients. Plotz and assoc. (19) established hypertension in 84% among a group of 33 patients, and in 85% of a total of 189 cases described in literature sources. In our series of patients, increased blood pressure is encountered in 90%. The higher incidence of hypertension established by the authors of the paper is very likely due to

Table 9

Distribution of Osteoporosis according to Severity, Sex and Form of Hyperadrenocorticism

			Without osteoporosis	Alignt osteorosis	Pronounced osteoporosis	Severe ostdoporosis	With bone dlformations	Total number of investiga-ted
Diencephalic syndrome	without hypertension	women	4	1	1	—	—	3
		men	1	—	2	—	—	
	benign hypertension	women	3	5	2	—	—	10
		men	—	3	—	—	—	3
	malignant hypertension	women	1	4	5	—	—	10
		men	—	—	—	1	—	1
Itsenko-Cushing's disease	without hypertension	women	3	—	2	1	1	7
		men	—	1	4	1	—	6
	benign hypertension	women	4	18	43	4	5	24
		men	1	1	10	—	6	18
	malignant hypertension	women	1	5	29	22	15	72
		men	—	—	14	3	10	27
Tumorous hyperadre nocorti-cism	without hypertension	women	3	—	—	—	—	3
		men	—	—	1	—	—	1
	benign hypertension	women	7	1	9	2	—	19
		men	1	—	1	—	1	3
	malignant hypertension	women	3	—	3	3	2	11
		men	—	—	—	—	—	—
	Total		32	39	126	37	41	275

the rather prolonged and systematic observations and follow up of patients, carried out at the Endocrinological Institute at Moscow, enabling the detection also of transitory or hypertensive conditions in the course of the disease, characterized by a later occurrence.

It should be stressed in advance that our observations on the distribution of the patients by sex, namely, that female to male ratio amounts to 3.25 : 1, conform with those of Plotz and assoc. (19) (1 : 3), and differ from those reported by Forsham (7) who claims a 1 : 4 ratio. Our experience and that reported by Plotz are nearer the actual proportion, being the groups of patients studied by far more numerous.

Our observations upon the distribution of patients according to age conform in general oultine with those claimed by Forsham (7), who reached the conclusion that a greater number of the patients are in the third and fourth decade of life. And yet, the predilection of a still younger age in tumorous hyperadrenocorticism conditions should not be overlooked.

Of particular interest is the high incidence of malignant hypertension, noted in our series.

MacMahon, Close and Hass (quoted by 17) first in 1937 described the Cushing's syndrome in two cases, with the characteristic for malignant hypertension vascular changes, found post mortem. Subsequently, malignant hypertension in patients with Itsenko-Cushing's syndrome was reported by

other authors too. Kincaid-Smith and assoc. (12) in their seires of 197 patients with malignant hypertension recorded only one case with Itsenko-Cushing's syndrome. Montgomery and Welbourn (15) established "malignant changes in the fundus oculi" in four out of a total of 15 patients with Itsenko-Cushind's syndrome.

According to the majority of writers (1, 12) malignant hypertension constitutes a phase in the development of various hypertensive diseases, with an incidence not exceeding 1 per cent of the total number of cases with hypertension. According to Perera (quoted by 12) this figure is 7 per cent. In compliance with data issued by the Therapeutical Institute in Moscow, development of malignant hypertension is observed in 1.5% of the total number of patients with hypertonic disease (3). Our investigations show that the incidence of malignant hypertension in hyperadrenocorticism amounts to 43.3% and moreover, that between the latter and the incidence of benign hypertension in the same condition no difference exists. It should be furthermore pointed out that the age distribution of patients affected by hyperadrenocorticism strongly resembles the age distribution of malignant hypertension (3, 9).

Contrary to malignant hypertension observed in common hypertensive conditions, affecting males more frequently (13, 9, 12, 16), our data prove that malignant hypertension in hyperadrenocorticism affect females and males with approximately equal incidence.

Welbourn (24) carried out comparative evaluation between the blood pressure in hyperadrenocorticism and the mean value of blood pressure among the healthy population, and found out that in all his patients, with the exception of systolic pressure in one woman and diastolic in two other, the blood pressure was higher than in healthy population. He could not reach more definitive conclusions on account of the relatively small number of patients personally studied (32).

The comparison of blood pressure with a) blood pressure in healthy individuals and b) in hypertonic disease reveals on the whole lower values of hypertension in hyperadrenocorticism, the latter tendency being particularly pronounced in the pulse pressure; the latter in all forms of hyperadrenocorticism is considerably lower than that in hypertonic disease, and in some instances (absence of arterial pressure rise, benign hypertension in males with Itsenko-Cushing's disease and in all cases of diencephalic syndrome) it is identical to that encountered among the healthy population. It should be emphasized that pulse pressure in females with hyperadrenocorticism is usually higher as compared to males (Table 5) — a difference not marked in ordinary hypertension ($t = 1.71$, $P < 0.1$).

For the time being the finding of an explanation of these facts appears to be rather difficult. Miasnikov (3) points out that the relationship-maximum and minimum blood pressure values-is influenced far and foremost by the elasticity of the major blood vessels' walls and by the contractile capacity of the heart. A reduced arterial elasticity accounts for simultaneous intensification of the increase of systolic and decrease of diastolic pressure. Mostly pronounced, this phenomenon is observed in atherosclerosis of the major arteries. It is known that changes in elasticity of the vascular walls bring about a rise in pulse pressure in hypertonia, whereas a weak cardiac muscle conditions the fall of pressure.

It is emphasized by the majority of authors (2, 7, 19, 13) that arteriosclerosis is an early and often met complication of hyperadrenocorticism. On autopsy material, studied by Plotz and assoc. (19), arteriosclerosis (ranging from tiny lesions of the aorta to severe generalized arteriosclerosis) was established in 50 of a total of 56 investigated intentionally hyperadrenocorticism cases. Maunix and Glenn (13) point out that in their series of 49 patients with Itsenko-Cushind's syndrome, hypertension was frequently associated to arteriosclerosis, regardless of the young age, occasionally revealing a generalized characteristic feature. Biopsy studies show that changes in the minor vessels of the kidneys were more pronounced than anticipated. A common roentgenological finding in our series is the elongated and sclerosing aortal arch. Anyway, contrary to expectations, the pulse pressure in most of the cases did not exceed that of the healthy population. It is believed that in the latter case the myocardium is more heavily involved, and its condition mostly determines the systolic-diastolic amplitude, all the more that according to Plotz (19), the fatal outcome in 27% of the patients is caused by heart failure. The lack of evidence for hypercholesteremia in most cases is a further prove for some peculiarities in the course of arteriosclerosis in hyperadrenocorticism (19). In accordance with the opinion expressed by Pickering (18), the participation of nerve factors is excluded from the mechanisms of increased blood pressure in the Itsenko-Cushing syndrome.

Also it is interesting to note the fact that in malignant hypertension, in males and females alike, where a weaker cardiac muscle is reasonably anticipated, the pulse pressure is highest.

In general, as already pointed out, the blood pressure in hyperadrenocorticism displays lower values than in hypertonic disease except for diastolic pressure in malignant hypertension in women and men alike, affected by Itsenko-Cushing's disease and tumorous hyperadrenocorticism.

The analysis of the data resulting from the comparative study of blood pressure in the different forms of hyperadrenocorticism, demonstrates that in malignant hypertension in females, the systolic pressure is not too high, contrary to diastolic pressure, which is significantly higher than that in benign hypertension. Malignant hypertension in males is distinguished by higher values and severer course. In diencephalic syndrome cases there is no difference in the values of blood pressure between malignant and benign hypertension; the difference between them is determined mainly on the basis of changes occurring in the fundus of the eye. It should be further emphasized that malignant hypertension, regardless of the generally heavy and progressive course of the Itsenko-Cushing's disease and tumorous hyperadrenocorticism, displays a milder and rather more favourable evolution as compared to malignant hypertension in other hypertensive conditions and the average lifespan is prolonged. It is known, that prior to the introduction of modern hypotensive means, the average life duration in malignant hypertension cases did not exceed one, maximum two years. It is rather difficult to establish with precision the average duration of life in malignant hypertension with our series of patients, but it is definitely much longer than two years. It is worth mentioning also that in the patients with Itsenko-Cushing's disease + malignant hypertension, studied more closely and in detail, a fluctuating course of the process is noticed, more particularly of the changes involving the fundus of the eye and blood pressure, with periods

of exacerbation alternating, especially after treatment, periods of remissions. The fluctuation described in the course of malignant hypertension accompanying the Itsenko-Cushing's disease is very similar to the course of rheumatism.

Our investigations demonstrate that the vascular process in hyperadrenocorticism, and especially in Itsenko-Cushing's disease, bears a generalized characteristics. An accurate confrontation of the renal function to the type and severity of hypertension was not possible with our patients. Nevertheless, as far as renal function could be judged by proteinuria, we were impressed that it was more heavily damaged in comparatively few patients. On the whole, the observations and investigations carried out in our patients with malignant hypertension, conform with the statements of Keith, Wagner and Kernoham (9), insofar in malignant hypertension the „characteristic" for the disease retinitis is associated to pronounced hypertension and adequate renal function. In nearly all cases of our series the heart was enlarged. The only exception are several patients with tumorous hyperadrenocorticism. It is interesting to note that increased cardiac dimensions were disclosed even in cases without elevated blood pressure. It is well known that hypertrophy of the heart in hypertension is a sign of a lasting and persisting rise of blood pressure. The enlarged cardiac dimension in the latter case should be ascribed either to undetected, long since present hypertension, or to primary weakness of myocardium (myocardia insufficiency).

The severeness and widespreading of osteoporosis in our patients is closely related to the type and severity of hypertension. Also it is interesting to note that in individual cases exhibiting wavy course of malignant hypertension, a parallel fluctuation is also observed in the severity of the osteoporotic process.

Casual relationship between the disturbances in the carbohydrate metabolism and the type of hypertension was not established in our patients. According to Plotz and assoc. (19) obvious diabetes is found in 15% of the patients with hyperadrenocorticism, whereas according to Forsham (7), this figure reaches 20%. We too established evident diabetes in 20% of the cases.

According to Racker and assoc. (20), the severity of hypertension in hyperadrenocorticism depends on the duration of morbidity. They add however, that exceptions from this rule are existant.

The analysis of the results of our investigations shows that such a dependence exists merely for malignant hypertension in males affected by Itsenko-Cushing's disease and tumorous hyperadrenorcoticism as well. It is worth mentioning that malignant hypertension in diencephalic syndrome cases is distinguished with the longest duration of the morbid condition; the latter represents a light form of the Itsenko-Cushind's syndrome, next coming the duration in Itsenko-Cushing's disease and tumorous hyperadrenocorticism, or in other words, the malignant hypertension in slight forms of hyperadrenocorticism is characterized by a prolonged course of morbidity. Thus it seems justified to assume that in the latter case a role is played not merely by the duration of the noxious action, but by its severity as well.

The pathogenesis of hypertension and malignant hypertension in particular in hyperadrenocorticism is as yet unclarified. Studies carried out by many writers (8, 14, 15, 18, 20, 24) show that surgical treatment of the Itsenko-Cushing's disease and tumorous hyperadrenocorticism restores blood

pressure within normal limits but, merely in cases in which surgery is in a position to exert a general effect on the morbid condition. In long lasting morbidity with deteriorization of the process and heavy involvement of the vessels and kidney, the blood pressure does not get normalized.

The exact mechanism of the blood pressure increase in hyperadrenocorticism, as already underscored, is unknown. Hypertension has been experimentally induced with the aid of various cortico-adrenal hormones, cortisol and cortisone included (11), with duely proved definitive role in the pathogenesis of the Itsenko-Cushing syndorme. There is also clinical experience on the development of malignant hypertension in the course of cortisone therapy (6, 22). In the Conu syndrome, usually brough about by hyperaldosteronism, increased blood pressure is likewise observed. Apparently, a variety of corticoadrenal hormones or combinations, among which also cortisol, are important insofar etiology is concerned for the development and for the characteristic features of hypertension in hyperadrenocorticism. The good results after timely carried out surgical management are an important argument in favour of this concept.

REFERENCES

1. Бозаджиева, Е. Вътрешни болести. 1965, 3, 293.
2. Васюкова, Е. А. Современные вопросы ендокринологии. 1960, Москва, 149—168.
3. Мясников, А. Л. Гипертоническая болезнь. Москва, 1954.
4. Пухлев, А. и сътруд. Кръвното налягане в българското население. С., 1964.
5. Сепетлиев, Д. Статистически методи за обработка на данни от медицинските научни проучвания. С., 1965.
6. Ihrenreich, Th. and collab.—*A. M. A. Arch. Path.*, 1951, 52, 145—54,
7. Forsham, P. H. The adrenals. Williams Textbook of Endocrinology. London. 1962.
8. Hoobler, S. W. Hypertensive disease. New York.
9. Keith, N. M. and collabor. — *Arch. Inter. Med.*, 1928, 41 : 141—188.
10. Keith, N. M. — *A. M. A. Arch. Inter. Med.*, 1965, 87 : 25—47.
11. Knowlton, A. J. and collab. — *J. Exper. Med.*, 1952, 96, 187.
12. Kincaid-Smith, R. J. and collab.—*Quart. J. Med.*, 1958, 27: 117—153.
13. Mannix, H., F. Glenn — *JAMA*, 1962, 180 : 225.
14. Mills, L. C. Hypertension, the first Hahnemann symposium on Hypertensive disease. London, 1959, 232.
15. Montgomery, D. and collab. — *Brit. J. Surg.*, 1957, 45 : 137.
16. Page, I. H. — *Ann. Inter. Med.*, 1939, 12 : 978.
17. Pickering, G. W. and collab. — *Lancet*, 1952, 2 : 952.
18. Pickering, G. W. High blood pressure. London, 1955, p. 276.
19. Plotz, Ch. M. and collab. — *Amer. J. Med.*, 1952, vol. 12 : 597—614.
20. Raker, J. W. — *Amer.. J. Surg.*, 1964, 107 : 153—158.
21. Schottstaedt, M., M. Sokolov — *Amer. Heart. J.*, 1953, 45 : 331—362.
22. Sharnoff, J. C. and collab. — *Jama*, 1951, 145 : 1230—1232.
23. Wagener, H. P., N. M. Keith — *Arch. Inter. Med.*, 1924, S4 : 374—387
24. Wellbourn, P. B. — *Brit. J. Surg.*, 1964, 51 : 738—743.

О НЕКОТОРЫХ ОСОБЕНОСТЯХ ГИПЕРТОНИИ ПРИ БОЛЕЗНИ ИЦЕНКО-CUSHINÇ И ПРИ ПЕРВИЧНОМ (ОПУХОЛЕВОМ) ГИПЕРКОРТИЦИЗМЕ

З. Бозаджиева

РЕЗЮМЕ

Кровяное давление исследовалось у 319 больных гиперкортицизмом, 40 среди которых с диэнцефальным синдромом, 225 — с тяжелой формой болезни Иценко-Cushing и 54 — с опухолевым гиперкортицизмом.

У 10% больных не было установлено наличия повышенного артериального кровяного давления, у 46,7% была доброкачественная гипертония и у 43,3% — злокачественная. Существенного различия в распределении гипертонии между доброкачественной и злокачественной не удалось установить. Злокачественной гипертонией были поражены в одинаковой степени как мужчины, так и женщины.

При сопоставлении кровяного давления с таковым при гипертонической болезни устанавливаются, в общем, более низкие цифры, причем эта тенденция ярче всего выявлена при пульсовом давлении, которое при всех формах гиперкортицизма значительно ниже, чем таковое при гипертонической болезни, а во многих случаях не отличается от такового у здоровых людей.